REMARKS/ARGUMENTS

After entry of this amendment, claims 1-46, 48, 50-76, and 78-80 are pending and claims 41-46, 48, 50-55, 71-76, and 78-80 are under consideration, claims 1-40, 56-70 having been withdrawn and claims 47, 49, and 77 having been canceled.

Claims 41, 44, and 74 have been amended to add a Markush group of Lewy body diseases. Support for this amendment is found at, *e.g.*, ¶133 of the specification. Claims 44 & 74 have also been amended to recite "the agent that induces an immunogenic response against alpha-synuclein is alpha synuclein or an immunogenic fragment thereof or an antibody to alpha synuclein" and "the agent that induces an immunogenic response against Aβ is Aβ or an immunogenic fragment thereof, or an antibody to Aβ." Support for these amendments is found at, *e.g.*, ¶¶ 14 and 16, and ¶20 of the specification, respectively. Claim 71 has been amended to recite "the agent that induces an immunogenic response against Aβ is Aβ or an immunogenic fragment thereof, or an antibody to Aβ." Support for this amendment is found at, *e.g.*, ¶20 of the specification. Thus, the claim amendments contain no new matter.

No claim amendment should be construed as an acquiescence in any ground of rejection. Applicants respond to the Examiner's comments using the paragraph numbering of the office action.

¶¶1-2. Applicants acknowledge the modification of the restriction requirement and that claims 41-48, 50-55 and 71-80 are now pending.

¶3. The term fragment has been deleted from claim 43 as redundant. The term "antibodies" as used in the specification includes intact antibodies and binding fragments thereof (*see* specification at ¶38).

¶¶4-39. Claims 41, 42, 45, 47, 48, 71, 72, 75, 77 and 78 stand rejected for obviousness-type double patenting over various Schenk patents in combination with Kotzbauer. The Schenk patents are cited as teaching methods of using an Aβ fragment and adjuvant to treat Alzheimer's

disease. Kotzbauer is cited as teaching co-existence of Lewy body pathology and Alzheimer's diseases. This rejection is respectfully traversed particularly as applied to the amended claims.

Kotzbauer discusses what is acknowledged in the background of the specification, namely, that some Lewy body disease patients and Alzheimer's patients have certain common pathological characteristics. However, as the specification points out, there are also distinct differences between the various disease including the predilection of specific brain regions and cell populations. Kotzbauer's discussion of the similarities is at the level of basic research and not tied to any therapeutic strategy. Kotzbauer provides no indication that therapeutic strategies directed to inhibition or reduction of Aβ deposits are likely to be successful in clearing synuclein deposits in Lewy body diseases distinct from Alzheimer's disease.

Probably in recognition of the above, it is noted that the Examiner has not applied the above rejection to claims reciting a specific Lewy Body Disease other than Alzheimer's, *i.e.*, Parkinson's (*e.g.*, claim 50). The present independent claims have been amended to recite a broader Markush groups of such Lewy Body diseases. It is respectfully submitted that these claims are distinguished from the cited references for the same reasons as the claims directed to Parkinson's disease.

¶40. Claims 41-43, 45-48, 50-55, 71-73 and 75-80 stand rejected under 35 USC § 112, first paragraph on the basis that the specification allegedly does not enable agents other than immunogenic Aβ. The Examiner alleges the specification does not enable antibodies or other agents. The Examiner's position is based on (a) need for repeated dosing of antibodies, (2) possible harmful immune response, such as mouse antibodies administered to humans, (3) peptides not being immunogenic, and (4) alleged unpredictability in the use of antibodies and other agents. This rejection is respectfully traversed particularly insofar as applied to the amended claims.

The amended claims now define the agent as Aβ or an immunogenic fragment thereof, or an antibody to Aβ. Thus, insofar as the Examiner's comments are directed to other agents they are moot.

The Examiner's comments regarding unpredictability of using antibodies to Aβ instead of Aβ itself appear to ignore the previous work of Schenk cited by the Examiner for double patenting. Schenk shows that antibodies to Aβ are effective in reducing deposits of Aβ in similar fashion to Aβ itself (*see, e.g.*, Examples XI and XII of US Patent No. 6,761,888). This result suggests that immunization with Aβ acts through the generation of antibodies. In light of this result and the present disclosure showing immunization of Aβ is also effective in reducing synuclein deposits, the skilled person would have no reason to doubt the present disclosure that antibodies to Aβ would be similarly effective to Aβ itself in reducing such deposits.

The Examiner's comment that passive administration of antibodies requires multiple dosing might be correct but does not provide a basis to question enablement. Similar considerations apply in any antibody treatment. There are several approved treatments in current use in which patients are dosed regularly. As of May 2004, there were about 17 approved antibody treatments on the US market (*see* Reichert & Pavlou, *Nature Reviews*, 3, 383-84 (2004), attached hereto).

The comments regarding immunogenicity of mouse antibody are also not a basis to question enablement. Although mouse antibodies are sometimes immunogenic, immunogenicity is not so universal or severe as to have precluded FDA approval of mouse antibodies for other indications. For example, the FDA has approved mouse OKT3 for treatment of acute transplant rejection. (*see* Reichert & Pavlou, *Nature Reviews*, 3, 383-84 (2004), attached hereto). Moreover, the solution to immunogenicity is well known in the art, and discussed in the specification, namely, the use of chimeric, humanized or human antibodies (*see* ¶¶ 75-83 of the specification).

The Examiner's comments regarding peptides not being immunogenic is over simplistic. Although peptide size may be a factor in the strength of immunogenic response, it is within the skill of the art, as summarized in the specification to obtain immunogenic responses with peptides by means of carriers and/or adjuvants. The Schenk patents cited for double patenting show that immunogenic responses can be obtained even for short Aβ peptides such as Aβ1-5 (*see e.g.*, Examples IV and V of US Patent No. 6,787,140).

¶¶51-61. Claims 44 and 74 stand rejected under 35 USC § 112, first paragraph on the basis that the methods are enabled only for immunogenic alpha synuclein and Aβ agents for essentially the same reasons as in the previous rejection under 35 USC § 112, first paragraph. Applicants respond as above.

¶¶62-67. Claims 41 and 71 stand rejected under 35 USC § 112, first paragraph for alleged lack of written description. The Examiner alleges that the specification lacks structural details for chemical entities. The Examiner alleges that such entities are only described by a desired function. This rejection is respectfully traversed particularly as it might be applied to the amended claims.

In the amended claims, the agent is Aβ or an immunogenic fragment thereof, or an antibody to Aβ. Reference to Aβ, a well characterized peptide, provides written description for AB itself and fragments thereof. Further, Example 6 of the *Synopsis of Application of Written Description Guidelines* and *Noelle v. Lederman* (cited by the Examiner) an antibody can be described by reference to a well-characterized antigen to which it binds. Thus, reference to Aβ also serves to provide written description of antibodies binding to Aβ.

¶68. Claims 43 and 73 stand rejected under 35 USC § 112, first paragraph for alleged failure to provide written description of antibodies to Aβ. The Examiner suggests that the specification must disclose a particular epitope specificity of Aβ. The Examiner cites *Noelle v. Lederman* as holding that an antibody can be characterized by its binding affinity to a well-characterized antigen. This rejection is respectfully traversed particularly as applied to the amended claims.

As *Vas Cath* makes clear, the relevant inquiry for written description is whether applicant was in possession of "whatever is now claimed." Here, what is now claimed are methods employing antibodies to a well-characterized antigen, in this case Aβ. As has been discussed above, the description of the antigen also provide written description for the antibodies binding to it. The Examiner's allegation that a narrower epitope within Aβ should be specified appears to be an issue of enablement rather than written description. However, in this case, the Examiner has not met his burden of showing why a particular epitope specificity would be

required. In previous work ((Bard et al., (2000) *Nat. Med.*, 6, 916-919, in which antibodies to Aβ have been used to inhibit or remove amyloid deposits of Aβ, it has been found that N-terminal antibodies are particularly effective for phagocytitic clearing of existing plaques. However, antibodies to other regions of Aβ have also been reported to have activity useful in inhibiting plaque development by binding to soluble Aβ in the circulation (DeMattos et al., (2001) *Proc. Natl. Acad. Sci. USA*, 98, 8850-8855 cited as cite no. AI by the IDS filed October 31, 2003)). In light of this background, the Examiner has not met his burden of showing that a particular epitope specificity would be required for use in the presently claimed methods.

¶¶76-81. Claims 44 and 74 stand rejected under 35 USC § 112, first paragraph for alleged lack of written description. This raises essentially the same issues as discussed in connection with paragraphs 62-67 of the office action and applicants respond as above.

¶82. Claims 43 and 73 are rejected under 35 USC § 112, second paragraph on the basis that the term "fragment" is allegedly indefinite. The term fragment has been deleted from these claims mooting the rejection.

¶¶83-86. Claims 41, 44, 45, 60, 71, 74 and 75 are rejected under 35 USC § 102(e) as allegedly anticipated by Jensen, US2002/0187157. Jensen is alleged to teach treating Parkinson's disease using an amyloid protein including Aβ and/or alpha synuclein. This rejection is respectfully traversed.

Jensen is mainly directed to administration of Aβ for the treatment of Alzheimer's disease. Jensen also mentions other "Alzheimer-like" diseases, including Parkinson's, Huntington's and prion-related diseases (*see* paragraph 247). However, Jensen does not disclose that the very same treatment for Alzheimer's disease (namely administration of Aβ) should also be given to the other diseases mentioned. Insofar as one can determine what Jensen is proposing, it would appear more likely he is proposing that other diseases be treated not with Aβ, the major peptide associated with Alzheimer's disease, but with whatever peptide plays a comparable role in the disease in question.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a prima facie case based upon the prior art (*In re Piasecki*, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984)). Here, the cited reference refers separately to Aβ and Parkinson's disease but never in the same sentence or paragraph or otherwise in a manner that clearly conveys an intent to administer Aβ for the treatment of Parkinson's disease. As discussed above, it is in fact unlikely that this was what Jensen intended. However, insofar as there is doubt on this issue, the doubt should inure to the benefit of the applicant given that the burden of proof rests with the Patent Office.

¶¶87-90. Claims 41, 44, 45, 50, 71, 74, and 75 stand rejected as allegedly anticipated by US Jensen, 2003/0086938. This rejection raises the same issues as discussed in responding to paragraphs 83-86 and applicants respond as above.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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